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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,544	12/20/2001	Bjorn Ludviksson	14014.0353U1	9811

23859 7590 05/07/2003

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	15

DATE MAILED: 05/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,544	LUDVIKSSON ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,8,9,11,18,19,21,24-26 and 29-43* is/are pending in the application.

4a) Of the above claim(s) *8,9,18,19,24,25 and 29-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,11,21 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/11/03 (Paper No. 14), is acknowledged.

2. Claims 1, 8-9, 11, 18-19, 21, 24-26, and 29-43 are pending.

3. Claims 8-9 and 18-19, 24-25 and 29-43 stand withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b) as being drawn to nonelected inventions.

4. Claims 1, 11, 21 and 26 are under consideration in the instant application as they read on a method of treating/preventing inflammatory bowel disease in a subject comprising adminstering to the subject a monoclonal antibody to αEβ7 and further comprising administering to the subject a monoclonal antibody to α4β7.

5. In view of the amendment filed on 3/11/03 (Paper No. 14), only the following rejections remained.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating of inflammatory bowel disease with αEβ7 Mab and further comprising administering an α4β7 Mab does not reasonably provide **enablement** for a method of **preventing** inflammatory bowel disease with αEβ7 Mab and further comprising administering an α4β7 Mab. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim essentially for the same reasons set forth in the previous Office Action mailed on 09/19/02 (Paper No. 10).

Applicant's arguments, filed 3/11/03 (Paper No. 14), have been fully considered, but have not been found convincing.

Applicant argues the specification on pages 19-20 discloses the administration of an αEβ7 is effective for both treatment and prevention of inflammatory bowel disease. Furthermore, the specification on page 10, lines 16-26 discloses that "the efficacy of an antagonist of αEβ7 in preventing an autoimmune disease, allergic disease, GvH disease or transplantation rejection can be determined by evaluating standard signs, symptoms and objective laboratory tests, as would be known to one of skill in the art, over time. .... strong family history of disease." Applicant concluded that one of skill in the art would clearly know how to assess the risk factors associated

with a particular subject and monitor the subject such that therapy for prevention of an autoimmune disease, such as inflammatory bowel disease, can be administered.

However, since the cause of inflammatory bowel disease (IBD) is unknown, it is unclear how to determine the subject in whom prevention is desired versus those in whom it is not desired.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1, 11, 21 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S Patent No. 5,610,281, in view of U.S. Patent No. 6,146, 630 and Hesterberg *et al.*

The `281 patent teaches a method for treatment, i.e. reduction or prevention (column 12, lines 9-13 in particular), of autoimmune disease, which is characterized by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin (column 6, lines 14-17 in particular). The `281patent teaches the treatment of ulcerative colitis (inflammation of the colon) (column 5, lines 56-63 in particular). Finally, the `281 patent teaches that agents that modulates adhesion between T lymphocytes (e.g., IELs) and E-cadherin expression cells are useful for targeting the delivery of therapeutic agents (column 5, lines 63-65 in particular).

The claimed invention differs from the reference teachings only by the recitation of the monoclonal antibody to αEβ7 in claims 11 and 11 and the monoclonal antibody to α4β7 in claims 21 and 26.

The `630 patent teaches a method for treating and preventing autoimmune adenitis (column 8, lines 24-25 in particular) using anti-integrin αEβ7 antibody wherein the antibodies can be monoclonal or polyclonal (column 3, line 5 in particular).

Hesterberg *et al* teach a method of ameliorating and treating an animal with chronic colitis with α4β7 Mab (abstract in particular). Hesterber *et al* further teach that the α4β7 Mab rapidly improved stool consistency and the α4β7 integrin represents a novel, potent and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract (see page 1379, last paragraph in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the peptide in the method of treatment or preventing taught by `281 patent with αEβ7 Mab taught by the `630 patent and α4β7 Mab taught by Hesterberg *et al* in methods of treating and preventing an inflammatory bowel disease as taught by `281 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because such antibody that modulates adhesion between T lymphocytes (e.g., IELs) and E-cadherin expressing cells are useful for targeting the delivery of therapeutic agents such as the antibody αEβ7 taught by the `281 patent and targeting α4β7 integrin represents a novel, potent, and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract as taught by Hesterber *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 3/11/03 (Paper No. 14), have been fully considered, but have not been found convincing.

Applicant argues that the `281 patent teaches the administration of an isolated peptide derived from the extracellular domain of E-cadherin, which binds to αEβ7 and inhibits the adhesion between an IEL and E-cadherin. Further, the disclosure of an interaction between αEβ7 and E-cadherin does not necessarily mean that administering a monoclonal antibody against αEβ7 would be successful in treating or preventing inflammatory bowel disease.

However, while αEβ7 can bind to other ligands in addition to E-cadherin as is evidenced by Ludviksson et al (J Immunol. 162(8):4975-82, 1999, IDS Ref. # A19) that 40% of αEβ7 cells bind to cells bearing E-cadherin (see page 4981, 1 column, top paragraph in particular). Applicant's specification and claims have not (a) count out the 40% inhibition and (b) the claims do not specify that the inhibition does not include the interaction between αEβ7 and E-cadherin.

10. The Declaration of Dr. Butcher under 37 CFR 1.132 filed 3/11/03 is insufficient to overcome the rejection of claims 1, 11, 21 and 26 based upon 35 U.S.C 103(a) as set forth in the

last Office action because: While the Examiner acknowledges that Dr. Butcher's Declaration provides some support that E-cadherin is not expressed to any appreciable extent in non-epithelial cells of the gut such as the lamina propia, where inflammatory bowel disease manifests itself. However, neither the instant claims nor the instant specification point out to the E-cadherin or any other counter receptors for the mucosal integrin αEβ7. Further, as noted above 40% of the αEβ7 cells bind to cells bearing E-cadherin in the lamina propia. Thus faced with the fact that 40% of αEβ7 cells bind to cells bearing E-cadherin, 60% of αEβ7 cells bind other counter receptors and the absence of claim language as to what counter receptor is being blocked, it is would be likely that an E-cadherin based mechanism would be successful for treatment of inflammatory bowel disease and it would have been obvious, at the time the present invention was made, to target the αEβ7 integrin to treat inflammatory bowel disease.

11. The following are New Grounds of Rejections.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

13. Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,455,042.

The `042 patent teaches a method of treating two inflammatory bowel diseases, ulcerative colitis and crohn's disease by administering an antibody to αEβ7 (see patented claims 1-4, column 47-48 in particular), wherein the antibody is monoclonal antibody (see column 15 lines 12-13 in particular). Ulcerative colitis and crohn's disease species anticipate the claimed inflammatory bowel disease genus. See MPEP 2131.02.

The reference teachings anticipate the claimed invention.

14. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S Patent No. 6,455,042 in view of Hesterberg et al (1997).

The teachings of the `047 patent have been discussed, supra.

The claimed invention differs from the `047 patent teachings only by the recitation of the method further comprising administering a monoclonal he antibody α4β7 in claims 21.

Hesterberg *et al* teach a method of ameliorating and treating an animal with chronic colitis with α4β7 Mab (abstract in particular). Hesterber *et al* further teach that the α4β7 Mab rapidly improved stool consistency and the α4β7 integrin represents a novel, potent and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract (see page 1379, last paragraph in particular).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to further add the monoclonal he antibody α4β7 to the method of treating IBD using the monoclonal antibody αEβ7.

One of ordinary skill in the art at the time the invention was made would have been motivated to because the α4β7 Mab rapidly improved stool consistency and the α4β7 integrin represents a novel, potent and organ-specific therapeutic target for the therapeutic modulation of inflammation in the gastrointestinal tract, as taught by the Hesterberg et al.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Further, "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose. . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205USPQ 1069, 1072 (CCPA 1980) (see MPEP 2144.06).

15. No claim allowed

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad, whose telephone number is (703) 306-3472. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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May 1, 2003

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